EXHIBIT 4

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

In Re: Methyl Tertiary Butyl Ether ("MtBE")
Products Liability Litigation

MDL No. 1358
Master File C.A. No.
1:00-1898 (SAS)

This document relates to the following case:
City of New York v. Amerada Hess Corp., et al.,
04 Civ. 3417

EXPERT REPORT OF KATHLEEN M. BURNS, Ph.D.

Methyl Tertiary Butyl Ether in Drinking Water and Public Health Protection

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February 6, 2009

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maintain a healthy pregnancy. It is therefore not surprising that MTBE studies in the early 1980s and those that followed, identified numerous developmental and reproductive system abnormalities (summary in CDC, 1996). The broad spectrum of harm that was observed in these studies is noteworthy, and the nature of birth defects and the poor survivorship observed in the studies that are discussed below is of high concern.

All developmental and reproductive toxicity studies were carried out in animals because it is unethical to intentionally expose people during pregnancy or childhood to chemicals not proven to be safe. Similarities between human development and that of other mammals support reliance on animal studies, which are required by the federal government for use in evaluating developmental toxicity and relied upon in evaluating reproductive and developmental risk (USEPA, 1996; USEPA, 1991).

Reproductive and developmental toxicity studies of MTBE conducted during the 1980s indicated a potential for harm both to the reproductive system of males and females and to their developing offspring. Two early studies are discussed in detail below because the results obtained and the way the results were reported were misleading with respect to the potential for harm, and they seriously undermined the ability of the public to be warned of the hazards of MTBE. These studies serve as just two examples of a larger pattern and practice of industry to report analytical data in such a way so as to obscure some of the most troubling results.

Biles et al.
In 1987, Biles et al studied parents and offspring over one-generation (meaning one reproductive generation) in rats. The industry-sponsored research had 15 individuals in each exposure group (each group that was given MTBE and one "control" group that was not exposed to MTBE). They were exposed to MTBE before and during pregnancy. Parents and offspring were then observed for reproductive damage. Kidney damage was observed (an increase of dilated kidney pelves) in the offspring of two exposed groups. In the second litter of pups, a six-fold (600%) increase in the mean number of pups who were dead at birth occurred, although the increase was not statistically significant.[13]

The authors reported that the rates were "comparable between control and treated groups" but failed to mention the increase in deaths. They also did not mention the renal damage, instead reporting only that pregnancy rates were lower for the second litter of pups, and that those results were not statistically significant.

The results showing the increase in the average number of pups dead with increases in MTBE

13. "Statistical significance" is a concept often used in science. It means that the results of a study were subjected to a mathematical test. The test can tell scientists something about the differences in the results between two groups that are being compared. In toxicology, the comparison is usually between a group of subjects who were not exposed to a chemical and those who were exposed. The results of the two groups are contrasted against each other. If a very small number of individuals were studied, it is exceedingly difficult to obtain statistical significance. In many cases industry used too small a number of study subjects. The small numbers meant that where industry observed alarming trends, they were able to ignore them as being statistically insignificant. If their goal was public health protection, they would have reported clear albeit statistically insignificant trends and acted upon the suggestive information in a protective manner by replicating tests with enough animals to determine whether the trends were significant or not.

exposure levels are shown in Table 2 below. They illustrate a problem with the way information is reported in this and other studies by industry. It is notable that the mean number of deaths generally increases with increasing MTBE exposure. This kind of relationship is an important observation because it supports the role of MTBE in causing the deaths. Such a relationship between increasing dose and increasing harm is evidence the government looks for when evaluating study results (USEPA, 2005) and is widely considered to be an important component of toxicological evidence.

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Table 2. Study by Biles et al, 1987: sample of results

Dose (ppm)	**0 (unexposed)**	**250**	**1000**	**2500**
mean number* of pups dead at birth	0.1	0.3	0.6	0.6

* Mean number refers to the average across all the litters at the specified MTBE exposure level.

The study authors did report a decreased pup viability index for the moderate and high dose group, but that involved only a small change (from 99 to 95.5 %) and so does not express the seriousness of the potential problem. "Viability index" is a term that would not be clear to many people. While viability in plain language means life or death, it is not expressed as such. In subsequent reporting of this study in a number of communications, the viability index is either not reported, or is dismissed as being unimportant.

A decrease in the survival of the pups after birth was also observed in the low and middle dose group. However, Biles et al (1987) conclude that:

> The effects of parental MTBE exposures were minimal to the offspring. The significant decrease in pup viability in mid and high dose groups of the F (1b) generation *is borderline* with respect to biological significance.

Biles et al (1987) also discussed survival indices (indicators of whether the pups lived or died) and concluded that the reduced pup survival "is *not believed to be a treatment-related effec*t."

In summary the industry-sponsored research paper stated:

> This present study indicates that an oxygenated hydrocarbon, MTBE, possesses little adverse reproductive toxicity potential as defined in a two litter, one generation reproduction assay in rats.

I disagree with the authors' statement that this study demonstrates MTBE "possesses little adverse reproductive toxicity" since many measures of early death were seen, as well as kidney abnormalities. These results taken as a whole should raise serious concerns about the potential impact of MTBE on human reproduction and development.

It is important to note here why the summaries themselves (as provided by Biles et al, and other industry researchers) are important. Studies such as this one are often very long and detailed,

having dozens of tables of results. Consequently, research studies usually provide a summary (also known as an abstract, executive summary, or by other titles). Most people who are not researchers rely on the summaries, especially if they don't have specialized training in toxicology. The information provided in the summary is absolutely essential and often forms the basis for decisions. Summarizations of results are perpetuated in latter discussions and in references to the study in other scientific papers, government and industry reports, and in technical arguments that support the establishment of protective standards (e.g., how much MTBE will be allowed in drinking water). The conclusions written in Biles et al in summarizing the study above continue to be perpetuated enabling the more troubling analytical data also contained in the report to go unnoticed.

In other words, the way that industry summarized the results of many studies of MTBE did not fully disclose the information such that the public and those in charge of protecting the public (e.g., regulators such as USEPA) could make fully informed decisions. Industry summaries were often misleading regarding results that suggested a problem, especially if the results did not achieve statistically significance. The communications with the public lacked critical information and portrayed MTBE in a more favorable light than was justified by the study results. Industry claims that MTBE had minimal potential for harm, a finding that would minimize the constraints the government placed on MTBE.

Circumstances surrounding this report are as troublesome as the misleading abstracts and conclusions. In addition to the problems with reporting results of the Biles et al reproductive study, records show that there were numerous serious problems with the way the study was conducted, including lost animals, incorrect assignment of gender, malfunctioning exposure equipment, a lack of carrying out the evaluation of some organ tissues, and incorrect reporting and analysis of results. These problems were identified in a quality assurance audit of the lab that performed the study, BioDynamics. A private firm retained by the AD HOC Steering Committee on MTBE reported to them on January 19, 1983 and February 16, 1983 (Hoover/API, 1983a and 1983b) about the serious problems with the study. The very serious errors made should have lead to the conclusion that the study results could not be relied upon for definitive answers regarding the potential for MTBE to cause reproductive toxicity. Given its limitations, it certainly could not be used to draw conclusions regarding MTBE's capacity to cause reproductive damage.

In spite of the fact that the poor quality of the study was known, and the observation of early pup death and other serious problems, the summary provided by Hoover/API (1983c) of this study reported that abnormal results were either not statistically significant or were "not considered to be significant." This summary would lead to the conclusion that MTBE did not pose the hazard of reproductive toxicity. In their summary this study was essentially written off as showing that there were no problems with MTBE in that regard - that it had been tested and found to be safe as far as having a potential to cause reproductive harm. *This is clearly and unequivocally not what the study found,* and that representation of results is wrong. It would lead the public and regulators to not take necessary actions to protect people from MTBE on the basis of a potential for reproductive harm.

I would conclude after reviewing the results that there appears to be, given the limitations of the

data, an impact of MTBE on pregnancy rates and the viability of offspring. I would note problems with the study and recommend it be redone with more animals so that statistical significance was more possible to achieve, and with far greater quality control of the study conditions. I would also not have drawn any conclusions regarding the lack of potential for harm, due to the study quality issues. The most responsible action for industry to do in this situation would be to replicate the study correctly.

Conaway et al.
Other industry-sponsored studies conducted by the same laboratory also had severe problems that were identified by an independent review of the laboratories practices. A study of birth defects[14] in mice and rats was performed, as reported by Conaway et al (1985). The laboratory quality assurance reviewers concluded that the laboratories report "is considered unacceptable based on the discrepancies noted" (in reference to the study carried out in rats, Hoover/API, 1983b).

In spite of the quality problems, the results of the study were published by Conaway et al in 1985. The study found that the number of live fetuses declined as MTBE exposure levels increased (statistically significant levels of change). It also found both internal and external birth defects (external and skeletal malformations) increased as the exposure level of MTBE increased, although statistical significance was not achieved. The kinds of skeletal abnormalities resulting from MTBE exposure included fused ribs (multiple ribs stuck together), angulated ribs (abnormal shaped ribs), and "scrambled" sternebrae (an abnormal but imprecise finding).

As with the previous study reported above, a relatively small number of animals were studied in each exposure group, making it very difficult to achieve a "statistically significant" result. Due to the inadequate number of animals tested, the results may not be considered “important,” even if it is clear a problem occurring. For example, in this study, there was a three-fold increase (300 %) in the percent of litters that had pups with birth defects. The actual count increased only from two litters with abnormal pups (with no MTBE exposure) to six litters having pups with abnormalities (in the high exposure group). Such a small numerical increase is unlikely to generate statistical significance, even though it seems quite important, and so the results are not reported.

Even with the very troubling results that were obtained, this study "concluded that MTBE administered by inhalation and the concentrations tested was not maternally toxic, embryotoxic, or teratogenic" (Conaway et al, 1985). This study was then and continued to be referred to as demonstrating that MTBE has no potential to cause birth defects.

The 1987 study by Biles et al summarized the results of this study as well, saying the Conaway study:

> produced no treatment related effects in maternal rates or their offspring and only slight increases in fetal resorptions and fused sternebrae in mice.

14 Teratology studies will be referred to under the broader heading of birth defects in this report.

The study results were also summarized by Hoover/API as showing no teratogenic responses (Hoover/API, 1983c).

These industry statements, in communications and in reports published in the peer-reviewed literature, were made in spite of skeletal abnormalities observed and the decrease in live fetuses. Use of qualifiers such as "slight increases" diminish the importance of the effects, which in this case are indicative of early mortality. This is clearly misleading and designed to trivialize outcomes that are far from trivial.

Studies in the late 1980s

In the late 1980s, additional studies at the Union Carbide Bushy Run Laboratories assessed the potential for MTBE to cause birth defects in a range of species: rats, mice, and rabbits. The study results were variously reported by Bevan, Tyl, Neeper-Bradley, and other researchers in 1989 (Tyl, 1989). They were not published in the peer reviewed scientific literature (accessible to all scientists and medical people) until 1997 (Bevan et al, 1997a and 1997b).

In the Bushy run study conducted in mice, MTBE caused very serious defects and death in the offspring. For example, the percentage of live fetuses was reduced from 93.9% to 64.5% (a loss of about a third of the fetuses). The body weights of the fetuses were reduced, and the number of fetuses with clubbed limbs, cleft palate, and dilated left ventricles (a heart defect) increased. These are all serious and substantial effects on offspring.

It is notable that the percentage of male pups declined. Although the cause for this has not been evaluated in any subsequent studies, the hormonal disruption caused by MTBE is of concern. Hormonal disruption has been associated with a skewing of the genders of children born in areas with chemical contamination. The evidence that MTBE causes hormonal disruption is discussed below.

Overall, the percentage of fetuses with birth defects (malformations) increased from 3.5% in the unexposed group to over 25% in those exposed to the upper dose of MTBE. *The percentage of birth defects that occurred steadily increased as the levels of MTBE increased* (Tyl, 1989). As noted previously, this is an important observation because this type of dose response dynamic is well-established indicator of a relationship between exposure and harm (Casarett and Doull's Toxicology, 1980)

Industry continued to report their study results in ways that were misleading and that did not adequately alert the public to the potential for MTBE to cause harm. Two examples are given below.

<u>Example 1.</u>

The way the information was reported is misleading and it is necessary to look at the details to see how this was accomplished. Skeletal defects are birth defects in the bones that occur in healthy unexposed animals and people with a low frequency. They vary in type from mild to severe, and range from delays in when the bones become fully formed and hard (consider the fontanels or soft spots on an infants head) to bones that form in odd shapes, are absent, or are present in higher

number than should be present. MTBE exposure caused both abnormal bone structures and delayed bone formation. These happened with increasing frequency as the MTBE levels increased, and important dose response observations that was noted above. Offspring who completely lacked bone formation in the "fingers"[15] of their front legs was 1.5% among the unexposed pups.

At the lowest exposure level of MTBE, the abnormalities increased to 4.5%, a tripling of the incidence of this defect. At the middle exposure level, the defects occurred in 6.1%, which is more than four times what was seen in offspring who were not exposed to MTBE. And at the highest dose of MTBE, more than one fifth of the offspring (21.2%) had no bone formation in their fingers. This was more than 14 times the rate seen in pups that were not exposed to MTBE (Tyl, 1989).

The 1989 industry study results showed many other types of harm with similar dose and response increases (Tyl, 1989). In spite of the progression of increasing harm as the dose increased, the study authors concluded that developmental toxicity occurred only at the middle and high dose, and reported only one specific defect, cleft palate. Cleft palate has long been recognized as being related to the toxic effects the mother was experiencing during exposure to MTBE, making it of less concern. That is the effect that they pointed to in their report and they ascribed the cause to maternal toxicity. The authors wrote in conclusion that *there were no effects on the offspring at the lowest dose tested*, in spite of the numerous trends that showed increases in harm at the lowest dose tested.[16]

It is important to explain why this is important. If there were an effect reported at the lowest dose tested, the actions of government and the requirements they could have place on industry would have been very different than what occurred. When harm is observed at the lowest dose, there was no way to determine an exposure level that won't cause harm (the "no effect level", even harm to the study animals. Because of this, federal policy requires that standards and other exposure limits include an additional safety factor of 10, meaning that the maximum amount of exposure would be reduced 10 fold. This has a substantial impact on the amount of a chemical allowed in air or water (USEPA, 1991, page 42) when exposure limits are based on the study that lacks a "no effect level".

Disclosure of increases in birth defects would likely have had other impacts on federal constraints placed on MTBE. Effects other than cleft palate would likely have been considered, and those could not as easily have been dismissed as simply byproducts of maternal toxicity. Due to the uncertainty involved with a no effect level, and the range of harm observed, the USEPA would like have requested more studies at a lower doses to determine if a "no effect level" could be identified and to more fully explore potential harm to children. Concerns about birth defects would have been greater, and if results were disclosed to the public (which becomes more likely if results aren't stated to show no harm), the public health community would like have questioned

15 "Interphalanges" is the technical term used in the report.
16 The authors were able to avoid reporting these troubling trends because results were not statistically significant. The statistical dilemma may be due to the small number of animals used.

the health implications of using MTBE in gasoline. Thus, in 1989, a candid reporting of these results could have resulted in constraints on industry's ability to expand its use in gasoline at that point in time.

Example 2.

Another example of the methods used to obscure critical information is illustrated by the way results were portrayed in a study by Tyl and Neeper-Bradley (1989). Table 3 shows the results for one type of birth defect reported in that study. Among normal unexposed pups, it is very common to find some bones that fail to completely form prior to birth. This occurred in half of the pups with no MTBE exposure, as Table 3 shows. It is also relatively common in the group that was tested that no bones are completely formed. This occurred in 40% of the unexposed pups. However, the study found that the percent of *pups that lacked bone formation increased as the MTBE exposure level increased.* At the highest exposure level over 80% of the pups lacked bone formation.

Table 3. Developmental Toxicity Study by Tyl, 1989: Sample of Results

Dose (ppm)	**0 (unexposed)**	**1000**	**4000**	**8000**
some bone formation	50.4	55.8	35.6	9.7
no bone formation	40.6	30.8	53.0	81.4
total percent with bone formation defect	93.7	94.4	93.2	97.9

The authors chose to group together some bone formation with no formation in their analysis, as shown in the last row of Table 3 above. Clearly an individual animal can't have both "some" and "none", so as the percentage of animals who lacked bone formation increased with MTBE exposure, the percentage with "some" bone formation had to decrease. If you sum together those who lack bone formation with those who have some bone formation under the broad heading of bone formation defects, it appears that MTBE is causing almost no effects. That is what the study authors did.

The results of the industry study were presented in their summary table showing similar responses between the MTBE-exposed pups and those with no exposure. As the numbers in the last row of Table 3 demonstrate, it looks like MTBE is not causing any problems. However, if the lack of bone formation was reported *separately*, as they should have been, a far different conclusion would have been obtained. *Attention would have focused on the ability of MTBE to interfere with the normal development of the skeleton.*

Both the authors' summary statement (given above) and a review of the final tallies in a summary table obscure the potential for MTBE to cause birth defects. Some or all of this study was conveyed to EPA on July 26, 1989. However, these results were a part of a 35 page report, and a review beyond the study summary by EPA staff with appropriate training in developmental toxicology may not have been carried out. The study was not publicly published in the peer-reviewed literature until 1997 (Bevan et al, 1997), making public scrutiny of the results prior to that time difficult at best.

During the same time period that the developmental studies were being carried out in the late 1980's, a study was conducted to evaluate reproductive harm over two generations by Neeper-Bradley, Dodd, Pritts, Fischer, Kubena, Panson, and Ridlon. The reproductive harm resulting from MTBE included a significant increase in the number of pups who died shortly after birth and lower body weights among the survivors during some developmental periods. These are clearly serious problems that merited scrutiny and follow up studies to better characterize why deaths were occurring. However, no additional multi-generation studies were carried out and the results were not published in the peer-reviewed literature until 1997 (Bevan et al, 1997). Important questions raised by the multigenerational study should have been fully aired and explored, and results be accurately provided via published studies available far earlier than 1997.

Study Design

Study design has a strong role in the ability of a study to identify harm by specifying whether an appropriate species is tested, how many subjects are used, and other characteristics. If a species is used that is especially resistant to certain types of harm, or if an inadequate number of animals are used, a study may not report harm, even though it is occurring. For example, authors can elect not to report results if results are not judged to be statistically significant. In many cases researchers will report the results with their statistical significance, even if the 95th percentile is not achieved. This brings essential scientific information forward and can suggest where additional work is needed. When researchers state that no statistically significant results were obtained, while still observing trends that indicate a potential for harm, it raises justifiable causes for concern among trained toxicologists and people who are responsible for protection of public health. And when study results that do suggest harm are summarized with a dismissal of effects, the results are predictable and favorable to arguments that there is no harm and that no additional testing is needed.

In fact, the summaries that dismissed or ignored results showing harm were used for decision-making. In 1986 when EPA was negotiating additional testing of MTBE, they concluded the following regarding reproductive and developmental effects:

> a. No treatment effects were noted when female rats were exposed to 0, 250, 1000, and 2500 ppm during days 6 to 15 of gestation (pregnancy).
>
> b. No dose-related adverse effects were noted in an inhalation study of the effects of MTBE on reproduction of rats through one generation.
>
> (USEPA, 1986).

If industry had fully disclosed their study results it is difficult to see how EPA would have reached this conclusion. Industry should have discussed the results and their implications and then carried out studies to fully explore the various types of harm that were identified in the reproductive, developmental, and multigenerational toxicity studies. In 2005, Billitti et al reported that MTBE caused "a gross disruption of the tubules within the testicles" in study animals. This means that the very small structures within testicles were harmed and indicates that MTBE can impair male

reproductive function.

Billitti also found that two metabolites of MTBE, TBA and TBF (tributyl formate) increased testis weight. As with the results above, this study provides evidence that MTBE can cause abnormal changes in the male reproductive system. The findings above are consistent with the results of studies from the early 1980s that showed MTBE had a potential to harm reproductive function. If the earlier studies had been taken seriously and the problems had been investigated fully, it is highly likely that widespread MTBE use and contamination would not have occurred.

Quality Control

Dr. Kirwin, was an industry toxicologist in charge of health and safety review of MTBE and participated in API and other industry meetings on MTBE's health effects. He made observations about many of the problems regarding the reproductive and developmental toxicity studies that were sponsored by the Defendants. He noted an inconsistency when the quality control auditor reported that the study laboratory erred in reporting no adverse effects, when there were in fact effects from MTBE (page 237 May 31, 2007 Kirwin Deposition). Dr. Kirwin identified the loss of animals as "a significant error" because it could result in a miscalculation of how many animals died (age 238, ibid). He also noted that not being able to determine which litters had missing pups or the number that were missing, or whether they were missing because they had abnormalities were "important quality control assurance concerns" (page 241 ibid).

Dr. Kirwin stated that that some of the problems identified in the internal quality control reviews would not have been sent to the reviewers within the government (page 243 ibid). In discussing peer review, he stated, "they (the reviewers) get the paper that is intended to be published." (page 303 ibid, reiterated page 25, June 2, 2007). In other words, the reviewers of a prospective journal article do not get information such as quality control reports on study problems, lost animals, misidentified animals or other reports that can call into question the accuracy of a study, unless the study authors chose to report those problems within a paper.

In fact, most of the numerous problems in the reproductive and developmental toxicity studies that were identified by quality control reviews and reported internally to the Defendants were not discussed in the papers that were published by the Defendants' scientists (e.g., Biles, Conway). Clearly, publication does not guarantee adequacy of the studies or accuracy in results. The scientists submitting the papers are relied upon to be accurately reporting their observations, and any problems that occurred during the studies.

The very serious nature of the problems that were observable in the Defendant's studies in spite of the limitations in the study is a very important issue when considering the developmental hazards of MTBE. Yet these studies were repeatedly referred to by the Defendants as showing that MTBE did not cause any particular hazards to pregnant women or children. In the absence of full information on the studies, having only the very limited information in the journal articles, this erroneous information was perpetuated and has misled the public regarding the true nature of the studies.

The reality of the situation did not suit the needs of the Defendants and so was not disclosed in

awareness of the problems associated with exposure to neurotoxins in early life.

Given the considerable evidence available early on regarding the neurotoxic properties of MTBE and the likelihood that public exposures would occur, industry should have carried out careful studies of neurotoxic impacts prior to adding MTBE to gasoline. Certainly, after receiving the results of the developmental studies described above and before widespread contamination had occurred, it would have been the responsible thing to do.

Recent Evidence Regarding Damage to the Male Reproductive System
In 2008 a study was published that provided additional evidence that males exposed to MTBE were at risk for damage to their reproductive system. Experimental evidence from short term (2 to 4 week) exposure studies found physical damage to the reproductive organs (Li et al, 2008). The tissues in the tubules used to carry sperm were damaged. The sperm themselves were also abnormal. Additional information was obtained on disruptions in numerous male hormones, as described below in the section on hormone disruption. Thus, the problems initially indicated in industry studies in the early 1980s have been confirmed. It is inexcusable from a scientific vantage point that the accurate information was not provided at that time, and that follow up did not occur quickly. MTBE's potential to disrupt and damage the reproductive system of males and the lack of any known safe level at which this will not occur, is a compelling reason to prevent public exposure to MTBE.

Summary Regarding Developmental and Reproductive Damage
The key conclusions that I draw from the information above are as follows:

- Studies of MTBE's developmental and reproductive toxicity during the 1980s provided evidence of many types of harm to the developing individual. The results in industry reports were misleading in stating that MTBE was not a developmental or reproductive toxin. This seriously undermined the ability of the public to be warned of the hazards of MTBE.

- The industry-sponsored studies were weak and in some cases had serious quality control problems. If these studies were done properly, they would clearly show a broad array of developmental damage based on the evidence that was available to industry in the 1980s.

Given the spectrum of developmental and reproductive hazards outlined in this section, it was not responsible to allow public exposures to MTBE to occur through introduction of MTBE to gasoline. Regarding the potential harm to children, it is both reasonable and prudent for water purveyors to seek to protect the public by minimizing exposure to MTBE to the best of their ability.

E. Cancer

The potential for MTBE to cause cancer has been evaluated in three long term exposure studies and in many follow up evaluations of specific issues related to carcinogenic potential. This highly

contentious area continues to be the subject of study, evaluation and scientific articles regarding the interpretation of data.

Basic Evidence that MTBE Causes Cancer.
The ability of MTBE to cause cancer has been researched in three basic studies of long term exposure and cancer outcomes. The basic cancer studies were carried out using both oral exposure (ingestion of MTBE) and inhalation of MTBE. This is important because some chemicals cause cancer when exposure occurs via one route, but not another. MTBE caused cancer in both exposure routes that were studied. The studies were performed at different laboratories by different researchers and studies were carried out on male and female subjects in two species. Table 4 lists the authors, study subjects, and types of cancer observed in the three basic cancer studies that were carried out. These formed the basis for discussions of MTBE's cancer-causing ability and for government actions.

Table 4. Studies of the Carcinogenicity of MTBE

RESEARCH AUTHORS	STUDY SUBJECTS	ORGAN SYSTEMS AFFECTED	STUDY SPONSOR	RESULTS DATES* (PUBLICATION)
Burleigh-Flayer, Chun, Kintigh	mouse	liver	industry	1991 (1997)
Burleigh-Flayer, Chun, Kintigh	rat	kidney, reproductive (testicular)	industry	1991 (1997)
Belpoggi, Soffriti, Maltoni	rat	reproductive (testicular), hematopoietic (lymphoma and leukemia)	Ramazzini Foundation	1995

* Dates results were given to study sponsors followed in parenthesis by date of publication in peer-reviewed journal, if those differ substantially. Burleigh-Flayer, Dodd, Bird, and Ridlon initially reported results of the mouse and rat studies 6/18/91, and they were released by Burleigh-Flayer, Chun and Kintigh as separate unpublished studies in 1992. They were published in 1997 in the peer-reviewed literature.

Study results showing statistically significant increases in cancer in two or more species meet important criteria established by USEPA for determining that a chemical is likely to pose carcinogenic risks to humans (USEPA, 2005). The observation of multiple types of cancers in multiple species that were exposed through different pathways provides additional information in support of a determination that a chemical is a carcinogen. The three studies listed in Table 4 formed the foundation for USEPA's past deliberations regarding MTBE's cancer causing abilities and some regulatory decisions. They are also fundamental to the decisions of many states, including New York, regarding MTBE in drinking water. The USEPA and state evaluation of MTBE regarding its cancer potential and their policy decisions are discussed in more detail below.[17]

17. The determination of MTBE's status as a carcinogen was and is very important in the context of policy and regulations, and this is discussed in Section V.

The cancer studies yielded differing results, but that is not surprising, given the different conditions of exposure and durations of the studies. The Belpoggi, et al study observed the animals until they died (a lifetime study), unlike the industry-sponsored studies. The lifetime observation provides an opportunity to observe tumors that occur later in life and that only occur at statistically significant levels when older animals are observed. This facilitates the identification of more tumors and different types of tumors than might otherwise be observed and may lead to higher estimated cancer potency for some chemicals (resulting in stricter controls). This information is undesirable if the goal is to keep a chemical on the market. However, it is optimal to fully evaluate potential public health impacts because we do care about health problems that may occur later in life.

It is well established in the cancer epidemiology literature that most types of cancer occur more frequently as people age. With rare exception, cancers are far more common among people in their 60s and 70s, than in young or middle-aged people (National Cancer Institute, SEER Database, available online at www.nci.gov). This fact was emphasized by Dr. Carroll Kirwin, Director of Health and Safety for many years at Phillips and the toxicologist who oversaw their evaluation of MTBE's health hazards. He recently stated with respect to doing chronic (long-term) studies that:

> Cancer requires lifetime exposures in these animals to reveal it. Cancer, as everybody knows, in general cancer is a disease of the aged, more old people get cancer than young people."
>
> (page 36, June 1, 2007 Kirwin)

Thus, the value of a full lifetime animal study is that it can identify the rate of occurrence of cancer, and the types of cancer more completely than studies that are terminated earlier in life. The Belpoggi et al (1995) study provides better insight into likely effects of MTBE, and their subsequent evaluations and publications regarding specific aspects of their study provide additional insights. In combination with the industry-sponsored studies that found cancer in two species, we have a group of studies that implicate MTBE as a carcinogen, and require that public exposures be minimized.

The last column in the table shows the dates that the study results were released to the study sponsors, followed by the dates that results were published in peer-reviewed journals that provide public access to the information. It is notable that there was a substantial delay between the first reporting of results of the industry-sponsored cancer studies in 1991, and the publication of the results in a manner that was accessible for review and use by the scientific community (1997). During that time period, MTBE moved from relatively limited use as an octane enhancer to very widespread use as the industry's oxygenate of choice to comply with RFG requirements. Industry elected to go forward with a substantial expansion in the production and distribution of MTBE in spite of the results of their own cancer studies.

Additional information that supports the positive cancer findings is discussed below under the heading "Mutagenicity and Genotoxicity". This information provides scientific insights into how

MTBE causes cancer. The supporting evidence makes it clear that MTBE causes damage at the cellular level, where cancer begins, and it does so through damage that we know can cause cancer. Overall, the objective evidence that MTBE can cause cancer is substantial and persuasive.

Additional Studies, Evaluations, and Debates Regarding the Basic Cancer Studies
The publication of the basic long term exposure studies that found MTBE caused cancer were followed by many papers discussing the results and reporting on new results that considered specific aspects of the types of cancer that were observed. Studies to evaluate mechanisms of carcinogenic action, provide more detailed pathological characterization of the tumors observed, and more fully evaluate the nature of the carcinogenic response. Many of these were funded by industry. Numerous studies in 1996 alone evaluated aspects of liver cancer (Moser et al, 1996), kidney cancer (Prescott-Mathews et al, 1997) and kidney cell proliferation, a precursor to cancer (Poe and Borghoff, 1996).

Industry has consistently maintained that MTBE was not carcinogenic to humans on the basis of a range of arguments addressing each of the types of cancer identified in the basic studies. In the discussions of these cancer studies, communications with the USEPA, and in scientific journals, industry has argued that MTBE does not pose a cancer risk to humans, in spite of strong evidence to the contrary. The basis for most of the arguments hinge on detailed and specific scientific characteristics of the tumors, mechanisms of tumor formation, characteristics of specific species, and statistical and quantitative issues. I have carefully reviewed these arguments and find them to be of questionable scientific validity and as such, that they do not undermine the need for protection from MTBE as a carcinogen. Of the dozens of articles on this issue, I have described a few below that are indicative of the general approach taken by industry to discount their own two studies and the additional study that found cancer was caused by MTBE.

A paper published by industry scientists in 1997 (McKee et al) argued that instead of using the rates of cancer that were found in control subjects in the industry study carried out in rats, they should rely on older studies that found different rates. This would allow them to dismiss the testicular tumors that occurred at statistically significant levels in their study among animals exposed to MTBE. It is both inappropriate and misleading to dismiss the results of a study by simply referring to what has happened in the past. In their study, where the exposed and unexposed animals were all treated in the same way and were from the same strain (being genetically nearly identical), a comparison of cancer occurrence among the animals was the most relevant. That comparison found significant results.

Dismissing the results based on historical data is not justified. In their "Guidelines for Carcinogen Risk Assessment", USEPA states the following:

> Generally speaking, statistically significant increases in tumors <u>should not be discounted</u> simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average. Random assignment of animals to groups and proper statistical procedures provide assurance that statistically significant results are unlikely to be due to chance alone.

(USEPA, 2005).

USEPA's statement echoes long-held scientific practices and indicates that the observation in 1991 of testicular cancer should have been taken far more seriously by industry if they were concerned about protecting the public. It is important to also note that testicular tumors were reported in the cancer study by Belpoggi et al (1995). This added corroborating evidence from industry's own study regarding testicular cancer, through similar findings in another study at a different laboratory carried out by a different set of researchers.

Another issue that has been raised involves alpha-2-microglobulin and kidney cancer. Industry argues that the kidney cancers should not be considered relevant because of this issue as it relates to male rats. In response to this, the National Science and Technology Council's team of government scientists studying the MTBE scientific evidence asserted that the industry arguments were only relevant to male rats. They noted that alpha-2-microglobulin was not involved in some important aspects of kidney damage in the study subjects (National Science and Technology Council, 1997).

More recently arguments have been made that because animals were followed for their entire lifespan in the Belpoggi et al study (1995), a calculation was required to adjust for survival times and subsequently modify the study's results. Industry scientists used a lifespan of 174 weeks in their calculations, which is much longer than the animals typically live. Two years, or 102 weeks, is the standard laboratory observation period in a life time study. By choosing a nonsensical number, they were able to manipulate the calculations to show results were not significant (Goodman et al, 2008).[18]

In practice, the industry scientists' calculations made no sense. The inappropriate assumptions they used were identified and described by cancer scientists working for the US National Institutes of Health, including the Director of the Office of Risk Assessment Research and the Associate Director for Chemical Carcinogenesis at the National Institutes of Environmental Health Sciences (Kissling et al, 2008). The government's top cancer scientists point out that the actual times of death that could have been used by the industry scientists to correctly use incorporate survival information have been available to the public for some years and are posted on a public website with the results of the study.

The government cancer experts carried out an analysis using a survival adjustment, but also employing a more standard length of life (the standard two years considered in most cancer

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18 The paper asserting changes were needed in calculations can be justifiably attributed to industry, though the affiliations of the authors were not oil companies, they were consulting firms. The acknowledgements section of the paper contains a disclosure that has increasingly been required by journals in the last few years - a statement of where the funding for the work and development of the paper comes from. The acknowledgement states:

> "Financial support for the research and preparation of this paper was provided by a fund created by various members of the oil industry engaged in litigation regarding the use of MTBE in gasoline." (Goodman et al, 2008)